Sensitization of the Skeleton to Vitamin-A Overdosage by Cortisol

By HANS SELYE

The simultaneous administration of cortisol and vitamin A to albino rats resulted in intense bone absorption not observed with vitamin A alone. The action of glucocorticoids was shown to be the opposite of the action of somatotropic hormones in respect to injury resulting from hypervitaminosis A.

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OUR EARLIER OBSERVATIONS have illustrated by many instances that an excess or deficiency of a hormone, which does not produce disease, may still regulate ("condition") disease susceptibility. Through this conditioning, hormones can play a decisive role in the development of pathologic lesions resulting from non-hormonal agents. The importance of this type of endocrine participation was first clearly demonstrated in the case of inflammatory, necrotizing and anaphylactoid reactions.[4,6]

More recently it was possible to show that hormones may also play a decisive conditioning role in determining susceptibility to non-inflammatory diseases. Osteolathyrism is an experimental malady characterized by degenerative and proliferative changes in the junction-cartilages as well as by the development of excessive periosteal bone. It was found that this disease can be prevented by treatment with ACTH or glucocorticoids and aggravated by somatotrophic hormone (STH) or luteotrophic hormone (LTH). Conversely, hypervitaminosis-A, which produces excessive bone absorption (for literature, see Fell,[1] Lowe and Morton[2] and Nieman and Klein Obbink[3]), can be prevented by the concurrent administration of STH.[5]

In view of these findings, it seemed of interest to determine whether a glucocorticoid could sensitize the skeleton for the osteoclastic bone absorption that normally takes place under the influence of excessive doses of Vitamin-A because, in general, STH and glucocorticoids tend to antagonize each other as regards their influence upon a variety of morbid changes.[4]

MATERIALS AND METHODS

Forty female Sprague-Dawley rats with an average initial body weight of 100 Gm.

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(range 96–106 Gm.) were subdivided into four equal groups: *Group I,* untreated controls; *Group II,* Vitamin-A; *Group III,* cortisol; *Group IV,* Vitamin-A and cortisol.

Vitamin-A was administered in the form of its palmitate at the daily dose level of 20,000 I.U. in 0.4 ml. of sesame oil, by stomach tube.

Cortisol (hydrocortisone acetate) was injected subcutaneously in the form of microcrystals at the daily dose of 1 mg. in 0.2 ml. of water. (A trace of Tween 80 was added to the aqueous medium in order to facilitate suspension.)

Throughout the experiment the rats were fed on "Purina Fox Chow." All animals were killed on the 20th day of treatment. Immediately after autopsy, the lower extremity of the right femur was fixed and simultaneously decalcified in Susa solution for subsequent histologic study of paraffin-embedded sections stained with hematoxylin-eosin. Then, the rest of the skeleton was carefully inspected in each case, special attention being given to the femur (as an example of a typical tubular bone) as well as to the scapula and the mandible, which are particularly predisposed to bone absorption during hypervitaminosis-A. The intensity of bone absorption was assessed both macroscopically and microscopically in each case.

Results

During the 20 days of treatment, the dose of Vitamin-A which had been administered in this experiment caused little, if any, detectable manifestations of bone absorption and, of course, cortisol alone likewise failed to produce the characteristic remodeling of the skeletal structures that occurs during intense Vitamin-A overdosage. On the other hand, all the animals which received Vitamin-A in combination with cortisol exhibited extraordinarily pronounced skeletal lesions.

Macroscopic inspection revealed intense remodeling of the femur with absorption of the shaft-tissue, especially in the distal two-thirds of the bone,

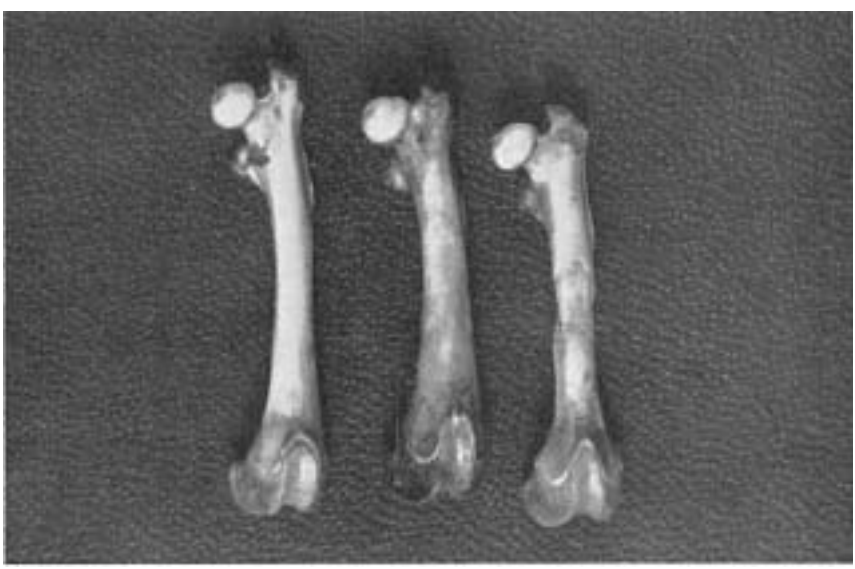

FIG. 1.—Femurs of rats treated with Vitamin-A alone *(left),* cortisol alone *(middle)* and Vitamin-A plus cortisol. Note that bone absorption is detectable only in the femur of the animal that has received Vitamin-A during sensitization with cortisol. The bone absorption is particularly evident in the lower two thirds of the shaft.

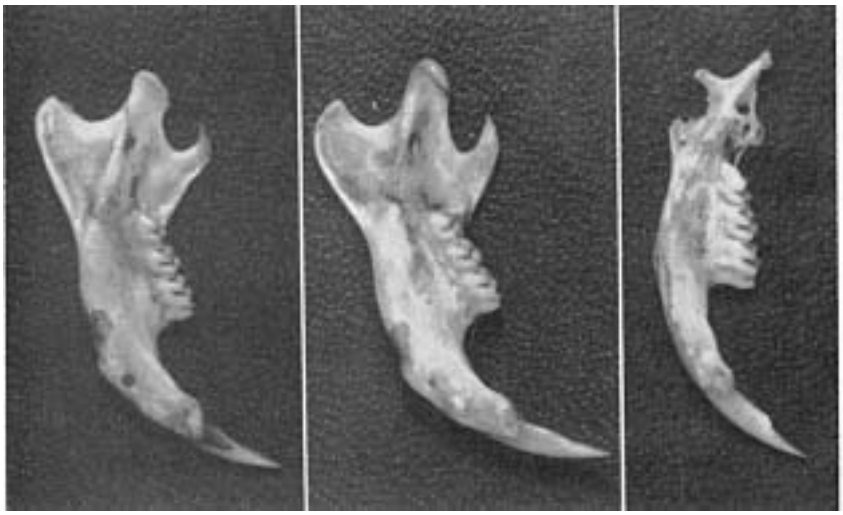

FIG. 2.—Mandibles of rats treated with Vitamin-A alone *(left)*, cortisol alone *(middle)* and Vitamin-A plus cortisol. Here, the bone absorption is particularly pronounced in the rat that has been treated with cortisol and Vitamin-A (the coronoid and condyloid processes as well as the angle of the jaw have virtually disappeared and the shaft of the bone is perforated in several places).

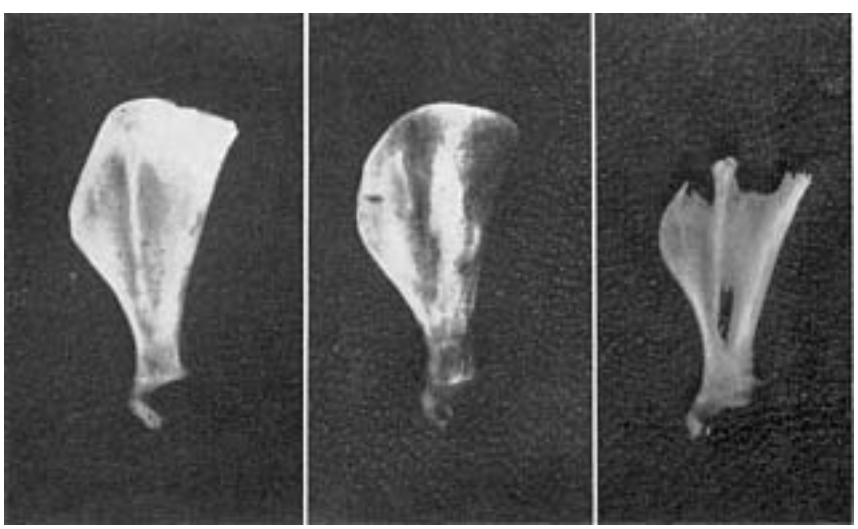

FIG. 3.—Scapulas of rats treated with Vitamin-A alone *(left)*, cortisol alone *(middle)* and Vitamin-A plus cortisol. Here, the synergism between cortisol and Vitamin-A is also clearly visible.

while the condyles themselves were not appreciably affected. The condyloid and coronoid processes of the mandible as well as the angle of the jaw had become extremely atrophic (in fact, these processes had virtually disappeared in several of the animals), and the bone was perforated by many holes. Similar surface erosions with perforations were visible in the scapulae (figs. 1–3).

Histologic observations revealed that the subperiosteal proliferation of osteoclasts that is characteristic of hypervitaminosis-A was particularly pronounced in all our rats treated with Vitamin-A in combination with cortisol. On the other hand, this change was absent in rats treated with cortisol alone, and either absent or at least of negligible intensity in those which were given only Vitamin-A.

Discussion

It is obvious from these findings that cortisol can greatly sensitize the skeleton to the characteristic manifestations of hypervitaminosis-A. Since, on the other hand, our earlier work had shown that STH counteracts the corresponding effects of an excess of Vitamin-A, it is evident that in this experimental lesion—as in so many previously studied diseases—the actions of glucocorticoids are opposed to those of STH.

Our findings show, furthermore, that in the syndrome of Vitamin-A intoxication, we have yet another example of a non-inflammatory morbid condition in which a change in the hormonal milieu can abolish or accentuate susceptibility to a non-hormonal pathogen.

Summary

Experiments on albino rats indicate that a moderate excess in Vitamin-A which, in itself, produces no detectable skeletal lesions, results in extraordinarily intense bone absorption, if the animals are sensitized to the Vitamin by simultaneous treatment with cortisol.

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